PHYSICAL CHEMISTRY 2016

13th International Conference on
Fundamental and Applied Aspects of
Physical Chemistry

Proceedings
Volume I

B E L G R A D E
September 26 - 30, 2016

ISBN 978-86-82475-34-7
Title: Physical Chemistry 2016 (Proceedings)
Editors: Željko Čupić and Slobodan Anić
Published by: Society of Physical Chemists of Serbia, Studentski trg 12-16, 11158, Belgrade, Serbia.
Publisher: Society of Physical Chemists if Serbia
For Publisher: S. Anić, President of Society of Physical Chemists of Serbia
Printed by: "Jovan", Printing and Publishing Company; 200 Copies.
Number of pages: 6+502; Format B5; printing finished in September 2016

Text and Layout: "Jovan"

200 - *Copy printing*

PHYSICAL CHEMISTRY 2016

13th International Conference on
Fundamental and Applied Aspects of
Physical Chemistry

Organized by

The Society of Physical Chemists of
Serbia

in co-operation with

Institute of Catalysis Bulgarian Academy of Sciences

and

Boreskov Institute of Catalysis Siberian Branch of
Russian Academy of Sciences

and

University of Belgrade, Serbia:

Faculty of Physical Chemistry
Institute of Chemistry, Technology and Metallurgy
Vinča Institute of Nuclear Sciences
Faculty of Pharmacy
Institute of General and Physical Chemistry, Belgrade, Serbia

International Organizing Committee

Chairman:	S. Anić (Serbia)
Vice-chairman:	M. Gabrovska (Bulgaria) A. A. Vedyagin (Russia) S. N. Blagojević (Serbia)
Members:	N. Cvjetićanin (Serbia), S. M. Blagojević (Serbia), M. Daković (Serbia), J. Dimitrić-Marković (Serbia), T. Grozdić (Serbia), Lj. Ignjatović (Serbia), D. Jovanović (Serbia), J. Jovanović (Serbia), M. Kuzmanović (Serbia), D. Marković (Serbia), B. Milosavljević (USA), M. Mojović (Serbia), N. Ostrovski (Serbia), N. Pejić (Serbia), M. Petković (Serbia), A. Popović-Bjelić (Serbia), B. Simonović (Serbia), D. Stanisavljev (Serbia), M. Stanković (Serbia), Z. Šaponjić (Serbia), B. Šljukić (Serbia) , G. Tasić (Serbia), N. Vukelić (Serbia), V. Vukojević (Sweden)

International Scientific Committee

Chairman:	Ž. Čupić (Serbia)
Vice-chairmans:	V. N. Parmon (Russia) S. Rakovsky (Bulgaria) B. Adnađević (Serbia)
Members:	S. Anić (Serbia), A. Antić-Jovanović (Serbia), G. Bačić (Serbia), R. Cervellati (Italy), G. Ćirić-Marjanović (Serbia), A. Cricenti (Italy), V. Dondur (Serbia), S. D. Furrow (USA), L. Gábor (Hungary), Vilmos Gáspár (Hungary), K. Hedrih (Serbia), M. Jeremić (Serbia), E. Kiš (Serbia), Lj. Kolar-Anić (Serbia), U. Kortz (Germany), T. Kowalska (Poland), V. Kuntić (Serbia), Z. Marković (Serbia), S. Mentus (Serbia), K. Novaković (UK), B. Novakovski (Poland), T. Parac Vogt (Belgium), M. Perić (Serbia), M. Plavšić (Serbia), G. Schmitz (Belgium), I. Schreiber (Czech Republic), P. Ševčik (Slovakia), N. Stepanov (Russia), M. Trtica (Serbia), V. Vasić (Serbia), D. Veselinović (Serbia), Á. Tóth (Hungary)

Local Executive Committee

Chairman:	S. N. Blagojević
Vice-chairmans:	A. Ivanović-Šašić A. Stoiljković
Members:	M. Ajduković, P. Banković, N. Bošnjaković, I. N. Bubanja, D. Dimić, A. Dobrota, J. Dostanić, A. Ignjatović, S. Jovanović, Z. Jovanović, A. Jović, N. Jović-Jovičić, D. Lončarević, M. Kragović, J. Krstić, S. Maćešić, J. Maksimović, V. Marković, D. Milenković, M. Milovanović, B. Nedić-Vasiljević, M. Pagnacco, A. Pavićević, N. Potkonjak, D. Ranković, M. Ristić, B. Stanković, A. Stanojević

STRUCTURE-ACTIVITY RELATIONSHIPS OF PROPAFENONE ANALOGUES ON *PSEUDOMONAS AERUGINOSA*: EXPERIMENTAL AND DOCKING STUDIES

M. Senćanski[1], B. Ivković[2], D. Božić[3], S. Grubišić[4], M. Milenković[3] and Z. Vujić[2]

[1]*Center for Multidisciplinary Research, Institute of Nuclear Sciences Vinca, University of Belgrade, Mihaila Petrovica Alasa 14, Belgrade, Serbia*
[2] *Department of Pharmaceutical Chemistry,*
[3]*Department of Microbiology and Imunology, Faculty of Pharmacy, University of Belgrade,*
Vojvode Stepe 450, Belgrade-Serbia. (blucic@pharmacy.bg.ac.rs)
[4]*Center for Chemistry, IHTM, University of Belgrade, Njegoševa 12, Belgrade, Serbia*

ABSTRACT

Series of six propafenone analogues has been evaluated for antimicrobial activities against *Pseudomonas aeruginosa*. Antimicrobial activity were confirmed for all tested compounds. The Docking studies of propafenone analogues into a X-ray crystal structures of porin Pseudomonas aeruginosa suggest that propafenone analogues show an interactions which may affect the functionality of porin i.e. bacterial cell.

INTRODUCTION

Earlier pharmacological studies discovered that propafenone analogues impair proliferation of cancer as well as microbial cells. Previous SAR studies of propafenone derivatives have selected the ethers, carbonyl, benzyl and amino groups as determinants for pharmacological activity of the propafenone and its derivatives [1-2]. Six of the synthesized derivatives are distinguished by the substitution of the benzyl moiety -F, -Cl atoms or –CH3, -CF3 groups (Table 1). These new substituents case significant changes of lipophilicity and stereoelectronic properties of the benzyl moiety. These structural modifications could result in formation of intermolecular bonds of the benzyl moiety of the propafenone derivatives with hydrophobic amino acid residues in the inner pore of the porin and enhanced antimicrobial activities.

EXPERIMENTAL

The X-ray crystal structures of porin *Pseudomonas aeruginosa* opdl PDB ID: 2Y0H [Crystal Structure of *Pseudomonas Aeruginosa* Opdl, Touw, D.S., Vijayaraghavan, J., Vandenberg, B., To Be Published] was obtained from the Protein Data Bank (http://www.rcsb.org/pdb). Compounds 1-7, Table 1, were constructed in Accelrys Draw 4.2 [3], protonated at pH 7.4 and geometrically optimized at MM level of theory using MMFF94 force field. Obtained structures were, along with protein structure, prepared for docking in Autodock Tools 1.5. Docking was carried in Autodock Vina 1.1.2. [4]. All calculations were carried on PARADOX computer cluster (Scientific Computing Laboratory of the Institute of Physics, Belgrade, Serbia).

RESULTS AND DISCUSSION

The binding site in porin, from docking results, consists of pocket between three inner loops, including following aminoacids: Val 123, Arg 124, Asp 121, Met 167, Leu 288, Thr 293, Thr 295 and Arg 296 (Fig. 1).

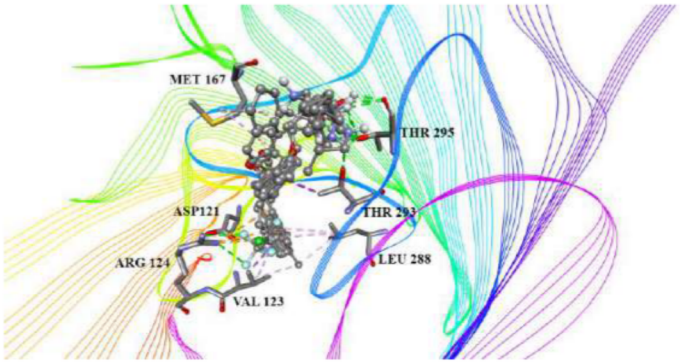
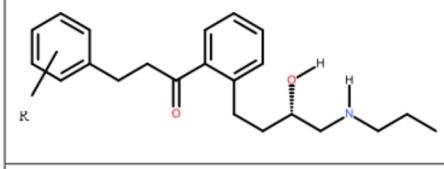


Figure 1. Binding site of porin with marked aminoacids, docked compounds and marked interactions. Green: hydrogen bonds, orange: electrostatic interactions, purple: alkyl-Pi interactions, pink: hydrophobic alkyl-alkyl

Having this series of compounds, Table 1, analogues of **PRO 12,** which differ only in substituent group and its position on aromatic ring, from docking poses analysis we can divide protein-ligand interactions into those that are common and subdivision of those determining the activity of compounds.

Table 1. Structures with measured and calculated activities

compound	Structure  R	IC50 mM	lnIC50	*E
1. 5OF	2-F	1.27	-13.6	-7.3
2. 5CF3	2-CF_3	2.24	-13.0	-7.1
3. 5PF	4-F	1.27	-13.6	-7.3
4. 5PCH3	4-CH_3	1.28	-13.6	-7.9
5. 5OCH3	2-CH_3	2.56	-12.9	-7.7
6. PRO	H	2.66	-12.8	-7.2
7. 5OCL	2-Cl	1.22	-13.6	-7.3

*E-vina binding energy, kcal/mol

Thus, all compounds from series form following stabilizing hydrogen bonds with residues Thr 295 and Thr 293, via protonated nitrogen atom or hydroxyl group. Moreover, there are stabilizing hidrophobic interactions, originating from Sulfur-Pi with Met 167, alkyl-Pi with Val 123 and Leu 288, and cation-Pi with Arg 124. Pi-alkyl interaction is also possible with methyl group of Thr 293. There is also found anion – Pi interaction with Asp 121. Mentioned subdivision consists of Arg124, Leu 288 and Val 123. As one can see from Table 1, compound with lowest activity is **PRO**, which has no substituent groups. The very close activity, somewhat higher has **5OCH3,** which includes methyl group in *ortho*- position. The explanation for this small difference could be presence of methyl group, which can contribute to stabilization in hydrophobic pocket, close to Val 123 and Leu 288. On the other hand, **5PCH3** has higher activity, for the methyl group is closer to hydrophobic binding pocket, forming more stabilizing interactions. In compounds pair **5OF- 5PF**, there is no significant difference, for the stabilizing electrostatic interaction – hydrogen bond is formed between fluorine group and Arg 124. The position of Arg 124 is such that difference in substituent position on aromatic ring does not affect the magnitude of interaction. The binding mode of **5OCl** is the same as **5OF** and the such small difference in activity can be neglected. Finally, **5CF3** has somewhat lower activity than **5OF** and **5OCl**, more similar to **5OCH3.** Although -CF3 group form stabilizing electrostatic interactions with Arg 124, its volume gives contribution to repulsive dispersive interactions with hydrophobic pocket, mostly with Val 123 and therefore lower activity is measured.

Binding energies as result from Autodock Vina are correlated with experimental values in manner of difference between *ortho- para-* pairs, ie **5PCH3 7** is calculated to be more active than **5OCH3**, which does not stand for different substituents with same position on aromatic rings (**5OF-5OCH3 - 5OCl).** However, the **5CF3** is calculated to have lowest activity and **5PCH3** to have the highest. This does not stand for **5OCl** and **5PF**, which are calculated to have same binding energy values, but much lower than **5PCH3**. This differences originate from docking program forcefield and under/overestimation of hydrophilic and hydrophobic interactions.

CONCLUSION

The performed docking studies studies of the propafenone derivatives indicates that their antimicrobial activity against Pseudomonas aeruginosa are realizing by modulating activity of porins.

Acknowledgement

This work was partially supported by the Ministry for Science of the Republic of Serbia (Grants no.172041 and No. ON171017).

REFERENCES

[1] Lowes D, Pradhan A, Lalitha V. et al. Lead Optimization of Antimalarial Propafenone Analogues, *J. Med. Chem.* **2012**, ***55,*** (13):6087–6093.

[2] Klepsch F, Chiba P, Ecker GFExhaustive sampling of docking poses reveals binding hypotheses for propafenone type inhibitors of P-glycoprotein., *PLoS Comput Biol*. 2011, **5**, e1002036.

[3] Avogadro: an advanced semantic chemical editor, visualization, and analysis platform, Marcus D Hanwell, Donald E Curtis, David C Lonie, Tim Vandermeersch, Eva Zurek and Geoffrey R Hutchison, Journal of Cheminformatics 2012, 4:17 doi:10.1186/1758-2946-4-17].

[4] O. Trott, A. J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization and multithreading, Journal of Computational Chemistry, 2010, **31**, 455-461.

CIP - Каталогизација у публикацији - Народна библиотека Србије, Београд

544(082)
66.017/.018(082)
502/504(082)
663/664:658.56(082)
615.31:547(082)

INTERNATIONAL Conference on Fundamental and Applied Aspects of Physical Chemistry (13 ; 2016 ; Beograd)
Physical Chemistry 2016 : proceedings. Vol. 2 / 13th International Conference on Fundamental and Applied Aspects of Physical Chemistry, Belgrade, 26-30 September 2016 ; [editors Željko Čupić and Slobodan Anić]. - Belgrade : Society of Physical Chemists of Serbia, 2016 (Belgrade : Jovan). - IV, 507-930 str. : ilustr. ; 24 cm

Tiraž 200. - Bibliografija uz svaki rad.

ISBN 978-86-82475-33-0

1. Society of Physical Chemists of Serbia (Beograd)
a) Физичка хемија - Зборници b) Наука о материјалима - Зборници c) Животна средина - Заштита - Зборници d) Животне намирнице - Контрола квалитета - Зборници e) Фармацеутска хемија - Зборници
COBISS.SR-ID 225802508

08. 09. 2016